SUPPLEMENT ARTICLE

Fluoroquinolone-Resistant *Campylobacter* Infections: Eating Poultry Outside of the Home and Foreign Travel Are Risk Factors

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A 12-month, population-based, case-control study of *Campylobacter* infections was conducted at Foodborne Disease Active Surveillance Network surveillance areas during 1998–1999. Of 858 *Campylobacter* isolates tested for antimicrobial susceptibility to the fluoroquinolone ciprofloxacin, 94 (11%) were resistant. Travel outside of the United States was reported by 27 (42%) of 64 patients with fluoroquinolone-resistant *Campylobacter* infection and by 51 (9%) of 582 patients with fluoroquinolone-susceptible *Campylobacter* infection (odds ratio [OR], 7.6; 95% confidence interval [CI], 4.3–13.4). When patients with domestically acquired fluoroquinolone-resistant *Campylobacter* infection were compared with matched healthy control subjects in a multivariate analysis, those infected were 10 times more likely to have eaten chicken or turkey cooked at a commercial establishment (18 [55%] of 33 case patients vs. 7 [21%] of 33 controls; matched OR, 10.0; 95% CI, 1.3–78). Although travel outside of the United States was associated with fluoroquinolone-resistant *Campylobacter* infection, most infections among study participants were domestically acquired. This study provides additional evidence that poultry is an important source of domestically acquired fluoroquinolone-resistant *Campylobacter* infection. Control measures should include efforts to improve food handling in commercial establishments.

Campylobacter is the most commonly reported cause of bacterial gastroenteritis in the United States, causing an estimated 2.4 million human infections annually [1]. When antibiotics are indicated for the treatment of *Campylobacter* gastroenteritis, the drug of choice is either a fluoroquinolone (e.g., ciprofloxacin) or a macrolide [2, 3]. The proportion of human *Campylobacter* isolates resistant to fluoroquinolones has been increasing in most regions of the world [4]. In the United States, this increase is occurring both among persons infected during foreign travel and those with domestically acquired infections [5]. Because poultry is the most frequently identified source of *Campylobacter* infections, it has been suggested that the increase in the proportion of human *Campylobacter* infections resistant to fluoroquinolones is due primarily to fluoroquinolones used in food animal production, particularly in poultry [4]. In the United States, the increasing prevalence of fluoroquinolone resistance in domestically acquired infections occurred after fluoroquinolones were licensed for use in poultry in 1995 [5]. Furthermore, fluoroquinolone-resistant *Campylobacter jejuni* isolated from patients with domestically acquired

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infections and from retail chicken products have included identical molecular subtypes [5]. We report here the results of a population-based study in which we assessed the contribution of consumption of poultry and other foods to infections with fluoroquinolone-resistant *Campylobacter* species.

SUBJECTS AND METHODS

The Foodborne Disease Active Surveillance Network (FoodNet) was initiated in 1995 as a collaborative effort between the Centers for Disease Control and Prevention (CDC), the US Department of Agriculture (USDA), the US Food and Drug Administration (FDA), and selected state health departments to better determine the burden of *Campylobacter* infections and other foodborne illnesses in the United States. During the study period, the population in the FoodNet catchment area was 20,723,982 (7.7% of the US population) and included Connecticut, Georgia, Minnesota, and Oregon, and selected counties in California, Maryland, and New York.

This case-control study of sporadic *Campylobacter* infections was conducted for a 12-month period during 1998–1999 in the FoodNet surveillance areas (also known as "FoodNet sites"). Each site devised a systematic sampling scheme that would enroll 200 infected patients. The names of these patients were obtained by active laboratory surveillance: 341 clinical microbiology laboratories in the FoodNet sites were identified and contacted at least monthly to ascertain all culture-confirmed *Campylobacter* infections.

During this study period, FoodNet sites in Minnesota and Connecticut required and New York requested that all *Campylobacter* isolates be submitted to the state public health laboratory. The other sites requested that a single clinical laboratory in the catchment area forward 1 *Campylobacter* isolate per week to CDC through the National Antimicrobial Resistance Monitoring System (NARMS) [6]. *Campylobacter* isolates were tested for susceptibility to 8 antimicrobials, including ciprofloxacin, by Etest (AB Biodisk). We defined fluoroquinolone resistance among *Campylobacter* isolates as an MIC of ciprofloxacin of $\geqslant 4$ μg/mL.

We defined diarrheal illness as infection in a person living in a FoodNet site who had a stool sample that yielded a *Campylobacter* isolate and who was not part of a recognized outbreak, and we defined diarrhea as $\geqslant 3$ loose stools in a 24-h period. Control subjects were persons without infection who were matched by age (0 to <6 months, 6 to <24 months, 2 to <6 years, 6 to <12 years, 12 to <18 years, 18 to <40 years, 40 to <60 years, and $\geqslant 60$ years) to the case patient. One control was obtained for each infected person; most controls were obtained from sequential telephone digit dialing. Controls for children <2 years of age were obtained from 2 additional sources: lists of potential controls generated either from the FoodNet site's birth registry or from a list of children who had been seen recently for healthy child visits by a case patient's physician.

Potential subjects were interviewed within 21 days of their stool sample collection date, and potential controls were interviewed within 7 days after the case patient's interview. Potential subjects were excluded if their diarrhea started >10 days before their stool sample was collected, if they were unreachable by telephone within 21 days after their stool collection date, or if they could not recall their illness onset date. Potential controls were excluded if they had diarrhea in the 28 days before their matching case patient's onset date. In addition, potential case and control subjects were excluded if they could not speak English, if they did not have a home telephone, if they or a household member had a confirmed case of *Campylobacter* infection in the 28 days before the date on which the potential case patient's stool was obtained, or if they were otherwise unable to complete the interview.

We obtained informed consent from all participants. A parent or guardian was interviewed if potential subjects were <12 years of age, and permission of a parent or guardian was obtained before interviewing persons 12–18 years of age. This study was conducted in accordance with guidelines for human research specified by the US Department of Health and Human Services.

Case patients were asked about their symptoms, hospitalization, number of school- or work-days lost, and illness treatment. Case patients and controls were both asked about antibiotic and antacid use as well as about any immunocompromising conditions or chronic illnesses they had in the 4 weeks before the case patient's diarrheal illness onset date. In addition, all subjects were asked about food and water consumption, child day care exposure, travel, animal exposure, and food-handling practices during the 7-day period before the case patient's onset date. For this analysis, we defined foreign travel–associated cases as *Campylobacter* infection in persons who had traveled outside the United States during the week before their illness onset, and we defined domestically acquired cases as infection in those who did not travel outside the United States during the week before their illness onset. We also constructed variables from other variables measured on the questionnaire. For example, we created the variable for whether a person ate chicken or turkey by combining participants' answers to separate questions about chicken and turkey consumption.

We used PC-SAS, versions 6.12 [7] and 8.01 [8], in all statistical analyses. We entered variables identified through univariate analysis as having *P* values of <.06 into a multivariate model using stepwise conditional logistic regression. We then calculated the population attributable fraction by using the proportion of case patients exposed to the risk factor [9]. CIs were computed for model-adjusted, exposure-specific attributable fractions using a jackknife procedure outlined by Kahn et al. [10].

RESULTS

During the study, 4000 cases of *Campylobacter* infection were identified in FoodNet sites. Isolates from 858 (22%) of the cases were tested for susceptibility to fluoroquinolones. Of the 858 isolates tested, 94 (11%) were fluoroquinolone resistant. The percentages of *Campylobacter* isolates that were fluoroquinolone resistant ranged from 5% (17 of 339 isolates) in Minnesota to 16% (48 of 292 isolates) in Connecticut. Of the 858 patients whose fluoroquinolone resistance status was known, 646 (75%) were interviewed and enrolled in the study. These 646 patients included 64 (68%) of 94 with fluoroquinolone-resistant *Campylobacter* infection and 582 (76%) of 764 with fluoroquinolone-susceptible *Campylobacter* infection. Age-matched healthy controls were obtained for 62 of the 64 interviewed patients with fluoroquinolone-resistant *Campylobacter* infection.

Of the 64 patients with fluoroquinolone-resistant *Campylobacter* infection who were interviewed, 2 were from California, 27 were from Connecticut, 4 were from Georgia, 3 were from Maryland, 17 were from Minnesota, 10 were from New York, and 1 was from Oregon. The median ages of patients with fluoroquinolone-resistant and fluoroquinolone-susceptible *Campylobacter* infections were 31 years (range, 4 months to 83 years) and 35 years (range, 3 months to 96 years), respectively.

The 64 interviewed patients with fluoroquinolone-resistant *Campylobacter* infection were compared with the 582 patients with fluoroquinolone-susceptible *Campylobacter* infection. We found that patients with fluoroquinolone-resistant *Campylobacter* infections were not more likely to have taken fluoroquinolones in the month before the stool specimen was obtained than were those with susceptible infections (2 [3%] of 64 persons with fluoroquinolone-resistant infections vs. 30 [5%] of 582 persons with fluoroquinolone-susceptible infections; unmatched OR, 0.6; 95% CI, 0.1–2.5). Subjects with fluoroquinolone-resistant *Campylobacter* infections were 7.6 times more likely to report having traveled outside the United States during the 7 days prior to illness onset than were those with fluoroquinolone-susceptible infections (27 [42%] of 64 vs. 51 [9%] of 582 subjects; OR, 7.6; 95% CI, 4.3–13.4).

We also found that foreign travel was a risk factor for fluoroquinolone-resistant *Campylobacter* infection, when comparing the interviewed fluoroquinolone-resistant *Campylobacter* patients with their age-matched healthy controls (27 [44%] of 62 patients with fluoroquinolone-resistant *Campylobacter* infections vs. 2 [3%] of 62 healthy controls; matched OR [MOR], 13.5; 95% CI, 3.2–57). Foreign travel–associated infections were distributed over most of the study period, with a peak in May (figure 1). Of the 27 patients with foreign travel–associated

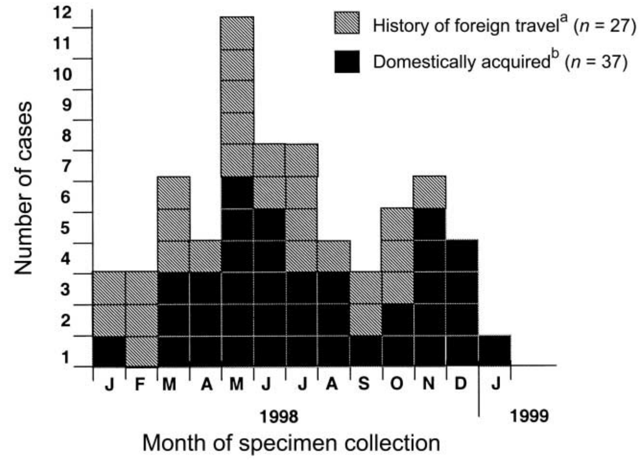

Figure 1. Cases of fluoroquinolone-resistant *Campylobacter* infection in Foodborne Disease Active Surveillance Network sites (Connecticut, Georgia, Minnesota, and Oregon and selected counties in California, Maryland, and New York), 1998–1999. [a]Traveled outside of the United States in the 7 days before the onset of illness. [b]Did not travel outside the United States in the 7 days before the onset of illness.

fluoroquinolone-resistant *Campylobacter* infection, 9 (33%) had traveled to western Europe, 7 (26%) had traveled to Mexico, 5 (19%) each had traveled to Asia and South America, and 1 (4%) had traveled to Central America.

Domestically acquired cases of fluoroquinolone-resistant *Campylobacter* infection were reported in all FoodNet sites. Patients with these infections accounted for 37 (58%) of the 64 patients with fluoroquinolone-resistant *Campylobacter* infection who were interviewed. Domestically acquired cases fluoroquinolone-resistant *Campylobacter* infection were documented in all months except February, with peaks occurring during May–June and November–December (figure 1).

The 37 patients with domestically acquired fluoroquinolone-resistant *Campylobacter* infection were more closely evaluated by comparing them with age-matched healthy controls. Using univariate analysis, we found that domestically acquired fluoroquinolone-resistant *Campylobacter* infections were associated with eating chicken or turkey cooked at a commercial establishment during the 7 days before illness onset, eating in a non–fast food restaurant during the 7 days before illness onset, and using an antacid during the 4 weeks before illness onset (table 1). Controls, however, were more likely than case patients to have eaten nonpoultry meat at home (table 1).

In our final multivariate model, we examined the following risk factors: eating chicken or turkey cooked at a commercial establishment, eating in a non–fast food restaurant, using antacids, and eating nonpoultry meat at home. Using this model, we found that eating chicken or turkey at a commercial establishment was the only risk factor that remained independently associated with illness (table 1). Patients with domestically ac-

Table 1. Exposures of patients with domestically acquired fluoroquinolone-resistant *Campylobacter* infection versus those of matched healthy controls in Foodborne Disease Active Surveillance Network (FoodNet) sites, 1998–1999.

	Study group, *n/N* (%)		Statistical analysis				
			Univariate		Multivariate		
Exposure[a]	Patients	Controls	MOR (95% CI)	*P*	MOR (95% CI)	*P*	PAF, %
Eating chicken or turkey cooked at a commercial establishment	18/33 (55)	7/33 (21)	6.5 (1.5–28)	.01	10.0 (1.3–78)	.03	38
Eating in a non–fast food restaurant	24/32 (75)	13/29 (45)	5.0 (1.1–23)	.04	…	…	…
Antacid use	9/33 (28)	2/33 (6)	4.5 (0.97–21)	.05	…	…	…
Eating non-poultry meat at home	17/33 (51)	26/33 (79)	0.1 (0.01–0.8)	.03	…	…	…

NOTE. FoodNet sites included Connecticut, Georgia, Minnesota, Oregon and selected counties in California, Maryland, and New York. *n/N,* no. of persons exposed/no. of persons for whom data were available; MOR, matched OR; PAF, population attributable fraction.

[a] Exposure to variables listed were during the 7 days before onset of diarrhea in case patients, except for antacid use, which was during the 4 weeks before onset.

quired fluoroquinolone-resistant *Campylobacter* infections were 10 times more likely to report having eaten chicken or turkey at a commercial establishment than were healthy control subjects (MOR, 10; 95% CI, 1.3–78); eating chicken or turkey at a commercial establishment accounted for 38% (80% CI, 3%–72%) of the population attributable fraction for domestically acquired fluoroquinolone -resistant *Campylobacter* infections. Domestically acquired fluoroquinolone-resistant *Campylobacter* infections constituted 58% of all fluoroquinolone-resistant infections. Therefore, 27% of all fluoroquinolone-resistant infections could be attributed to eating chicken or turkey in a commercial establishment.

DISCUSSION

Foreign travel is a risk factor for acquiring *Campylobacter* infection [11] and continues to be associated with fluoroquinolone-resistant *Campylobacter* infection. Several countries to which persons with fluoroquinolone-resistant *Campylobacter* infections traveled were in the developed world. Fluoroquinolone-resistant *Campylobacter* infections have been reported in numerous of developed countries, including western European nations [4]. The sources of travel-associated infections have not been studied but may be similar to those identified in investigations in several developed nations: undercooked poultry, contaminated water, raw milk, and cross-contaminated foods [12]. Fluoroquinolone-resistant *Campylobacter* infection should be considered in the differential diagnosis of traveler's diarrhea. Because of the potential for fluoroquinolone resistance, a macrolide is the treatment of choice for travel-associated *Campylobacter* enteritis.

Although we found foreign travel to be a risk factor for fluoroquinolone-resistant *Campylobacter* infection, most of such infections that we identified were domestically acquired; these infections occurred in all sites and in all age groups. Domestically acquired infections were associated with eating chicken or turkey in commercial food establishments. After removing travel-associated cases and controlling for other variables, we found that patients with fluoroquinolone-resistant *Campylobacter* infections were 10 times more likely to have eaten chicken or turkey in commercial food establishments in the 7 days before illness onset than were matched healthy control subjects. Almost one-half of the domestically acquired fluoroquinolone-resistant *Campylobacter* infections in this study could be attributed to eating chicken or turkey at a commercial establishment. These data and data from retail food sampling studies that have found fluoroquinolone-resistant *Campylobacter* organisms in chicken products at US grocery stores [5, 13] support the conclusion that poultry is the dominant source of domestically acquired fluoroquinolone-resistant *Campylobacter* infections in the United States.

Epidemiologic and laboratory data from several countries suggest that fluoroquinolone use in poultry is a major contributor to the increase in human fluoroquinolone-resistant *Campylobacter* infections [4]. Poultry has been documented repeatedly as a major food reservoir for human *Campylobacter* infections [12]. Experimentally, sarafloxacin treatment of chickens rapidly selects for fluoroquinolone resistance among *C. jejuni* [14]. Fluoroquinolone use in poultry and livestock is widespread in many regions of the world [4]. Although we did not evaluate such fluoroquinolone use this study, it is likely that many of the travel-associated cases may also be a consequence of fluoroquinolone use in food-producing animals. A temporal relationship between the licensure of fluoroquinolones for use in food animals, particularly poultry, and a subsequent increase in fluoroquinolone resistance has been documented in The Netherlands, Spain, the United Kingdom, and the United States [5]. Fluoroquinolone-resistant *Campylobacter* species have been isolated from retail chicken products in The Netherlands, Spain, Taiwan, the United Kingdom, and the United States [4]. In the United States, molecular subtyping has been used to identify otherwise indistinguishable strains of fluoroquinolone-resistant *C. jejuni* among isolates from patients with domestically-acquired *Campylobacter* infection and from locally available retail chicken products [5]. The results of our study add to these findings by specifically implicating poultry consumption outside the home as a risk factor for infection with fluoroquinolone-resistant *Campylobacter* species.

The association between eating poultry outside of the home and the risk for *Campylobacter* infection has been reported in other case-control studies of general *Campylobacter* infections [15–17]. One reason for this association may be that poultry-handling and poultry-preparation practices in restaurants may differ from those in homes. Although contamination levels in poultry distribution chains of restaurants and private homes may differ, it seems more plausible that food-handling errors in restaurants are at the root of the problem. Our findings suggest that if more attention was paid to food-handling practices in restaurants and other venues outside of the home, the number of fluoroquinolone-resistant *Campylobacter* infections could be reduced substantially. Assuming that all other exposures (known and unknown) remain constant, the average person's risk for fluoroquinolone-resistant *Campylobacter* infection could potentially be reduced by 27% if the risk associated with commercially prepared chicken and turkey were eliminated.

Many *Campylobacter* infections are likely to be treated with fluoroquinolones, and this use may result in an increased prevalence of fluoroquinolone-resistant bacteria. However, we found that fluoroquinolone use in humans did not contribute directly to the observed resistance: patients with fluoroquinolone-resistant *Campylobacter* infections were no more likely to have taken fluoroquinolones before stool specimens were obtained than were patients with fluoroquinolone-susceptible infections.

The burden of fluoroquinolone-resistant *Campylobacter* infection is substantial. Our finding that 11% of *C. jejuni* isolates are resistant to fluoroquinolones differs somewhat from the findings of the NARMS for Enteric Bacteria that fluoroquinolone resistance was present in 13.6% and 18% of *C. jejuni* isolates in 1998 and 1999, respectively [18]. Multiplying the 1998 figure (13.6%) by the total estimated annual number of *Campylobacter* infections (2.4 million [1]), we estimated that 326,000 fluoroquinolone-resistant *Campylobacter* infections occurred that year.

Mitigating efforts are needed to prevent the development of fluoroquinolone resistance in *Campylobacter* organisms in poultry. In October 2000, the FDA's Center for Veterinary Medicine proposed to withdraw approval for the use of fluoroquinolones in poultry in the United States [19]. This proposed measure will be an important step toward decreasing the number of fluoroquinolone-resistant *Campylobacter* infections among humans in this country.

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